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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup>:</b> <b>A61K 31/395, C07D 243/10, 243/38</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 98/11893</b> <b>(43) International Publication Date:</b> 26 March 1998 (26.03.98)
<b>(21) International Application Number:</b> PCT/US97/16586 <b>(22) International Filing Date:</b> 18 September 1997 (18.09.97) <b>(30) Priority Data:</b> 60/026,486 23 September 1996 (23.09.96) US <b>(71) Applicant (for all designated States except US):</b> ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> LARSEN, Samuel, D. [US/US]; 3088 Hamilton, West Lafayette, IN 47906 (US). NICHOLS, John, R. [GB/GB]; 62 Lynton Drive, Hillside, Southport, Merseyside PR8 4QQ (GB). REUTZEL, Susan, M. [US/US]; 4824 Eagles Watch Lane, Indianapolis, IN 46254 (US). STEPHENSON, Gregory, A. [US/US]; 10227 Bent Tree Lane, Fishers, IN 46038 (US). <b>(74) Agents:</b> PALMBERG, Arleen et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).		<b>(81) Designated States:</b> AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> OLANZAPINE DIHYDRATE D		
<b>(57) Abstract</b>  The present invention provides the novel Dihydrate D 2-methyl-thieno-benzodiazepine and a formulation therefor.		

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## OLANZAPINE DIHYDRATE D

This invention relates to the crystalline dihydrate D of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine (referred to herein as "olanzapine"). The invention more specifically relates to a novel crystalline form which is particularly useful for preparing an aqueous olanzapine formulation.

The stable crystalline Dihydrate D is particularly important for the commercial development of new formulations of the pharmaceutically active olanzapine. Olanzapine is useful for treating psychotic patients. Often an aqueous formulation or a formulation that is prepared using aqueous mixing is desired. Applicants have discovered that Form II olanzapine is the most stable anhydrous form of olanzapine, providing a stable anhydrous formulation with pharmaceutically desired characteristics. However, a stable dihydrate was desired to provide pharmaceutically elegant aqueous formulations.

A novel dihydrate crystal form of olanzapine has now been synthesized and characterized which possesses distinct advantages over the previously known forms, that is the material produced using the methods described in U.S. Patent No. 5,299,382 (hereinafter referred to as "the '382 patent"), when aqueous formulations or a stable aqueous intermediate is desired. This novel dihydrate crystal form is clearly distinguishable therefrom by x-ray powder diffractometry. U.S. Patent No. 5,229,382 is hereby incorporated by reference in its entirety.

Applicants have discovered that Dihydrate D olanzapine is essential to assure a pharmaceutically elegant, aqueous formulation. Applicants have found that olanzapine forms a Dihydrate B; however, this form appears

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to be quite unstable compared to Dihydrate D. Dihydrate D requires controlled conditions to prepare the substantially pure Dihydrate D material; however, once prepared, the Dihydrate D is surprisingly robust and stable. Therefore, Dihydrate D olanzapine is most desired and appears to be essential for use in preparing consistently stable commercial pharmaceutically elegant aqueous olanzapine formulations as well as for pharmaceutically elegant formulations prepared using extensive aqueous mixing.

The presently claimed invention provides the stable crystalline Dihydrate D olanzapine polymorph (herein referred to as "Dihydrate D") having a typical x-ray powder diffraction pattern as represented by the following interplanar spacings (d) as set forth in Table 1:

Table 1

d
9.4511
7.7098
7.4482
6.9807
6.5252
5.7076
5.5539
5.223
4.9803
4.8908
4.784
4.6947
4.4271
4.3956
4.3492
4.2834
4.1156
3.7837
3.7118
3.5757
3.482

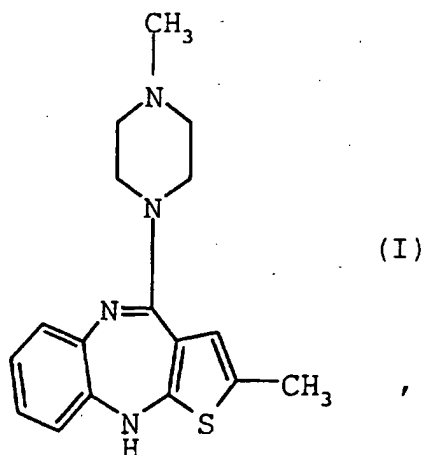
-3-

3.3758  
3.3274  
3.2413  
3.1879  
3.135  
3.0979  
3.016  
2.9637  
2.907  
2.8256  
2.7914  
2.7317  
2.6732  
2.5863

The x-ray powder diffraction patterns set forth herein were obtained with a copper k of wavelength = 1.541 Å. The interplanar spacings in the column marked "d" are reported in Angstroms. The detector was a Kevex silicon lithium solid state detector.

The present invention further provides an aqueous formulation comprising Dihydrate D as an active ingredient with one or more carriers or diluents therefor.

Applicants have discovered that 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine, which is a compound of Formula (I):



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exists as two different dihydrate forms which are distinguishable by x-ray powder diffractometry. The less stable, and therefore less desired dihydrate has been  
5 designated as Dihydrate B. Applicants have discovered that a stable dihydrate is necessary for the preparation of a consistently stable pharmaceutically elegant aqueous formulation. Both dihydrate forms are clearly distinguishable from the polymorph taught in the '382  
10 patent.

The polymorph obtainable by the process taught in the '382 patent is an anhydrate form which is not as stable as desired and not well suited for pharmaceutical formulations. The anhydrate obtainable by the process of  
15 the '382 patent will be designated as Form I and has a typical x-ray powder diffraction pattern substantially as follows, obtained using a Siemens D5000 x-ray powder diffractometer, wherein  $d$  represents the interplanar spacing:

$d$
9.9463
8.5579
8.2445
6.8862
6.3787
6.2439
5.5895
5.3055
4.9815
4.8333
4.7255
4.6286
4.533
4.4624

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4.2915  
4.2346  
4.0855  
3.8254  
3.7489  
3.6983  
3.5817  
3.5064  
3.3392  
3.2806  
3.2138  
3.1118  
3.0507  
2.948  
2.8172  
2.7589  
2.6597  
2.6336  
2.5956

A typical example of an x-ray diffraction pattern for Form I is as follows, wherein  $d$  represents the interplanar spacing and  $I/I_1$  represents the typical relative intensities:

$d$	$I/I_1$
9.9463	100.00
8.5579	15.18
8.2445	1.96
6.8862	14.73
6.3787	4.25
6.2439	5.21
5.5895	1.10
5.3055	0.95
4.9815	6.14

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4.8333	68.37
4.7255	21.88
4.6286	3.82
4.533	17.83
4.4624	5.02
4.2915	9.19
4.2346	18.88
4.0855	17.29
3.8254	6.49
3.7489	10.64
3.6983	14.65
3.5817	3.04
3.5064	9.23
3.3392	4.67
3.2806	1.96
3.2138	2.52
3.1118	4.81
3.0507	1.96
2.948	2.40
2.8172	2.89
2.7589	2.27
2.6597	1.86
2.6336	1.10
2.5956	1.73

The x-ray powder diffraction patterns herein were obtained with a copper  $K_\alpha$  of wavelength  $\lambda = 1.541\text{\AA}$ . The interplanar spacings in the column marked "d" are in  
5 Angstroms. The typical relative intensities are in the column marked " $I/I_1$ ".

A typical example of an x-ray diffraction pattern for the anhydrous Form II polymorph (see EP 733,635) is as follows wherein d represents the interplanar spacing and  
10  $I/I_1$  represents the typical relative intensities:



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d	I/I <sub>1</sub>
10.2689	100.00
8.577	7.96
7.4721	1.41
7.125	6.50
6.1459	3.12
6.071	5.12
5.4849	0.52
5.2181	6.86
5.1251	2.47
4.9874	7.41
4.7665	4.03
4.7158	6.80
4.4787	14.72
4.3307	1.48
4.2294	23.19
4.141	11.28
3.9873	9.01
3.7206	14.04
3.5645	2.27
3.5366	4.85
3.3828	3.47
3.2516	1.25
3.134	0.81
3.0848	0.45
3.0638	1.34
3.0111	3.51
2.8739	0.79
2.8102	1.47
2.7217	0.20
2.6432	1.26
2.6007	0.77

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As used herein "substantially pure" refers to Dihydrate D associated with less than about 20% Dihydrate B, preferably less than about 5% Dihydrate B and may preferably be less than about 2% Dihydrate B. Further, "substantially  
5 pure" Dihydrate D will contain less than about 0.5% related substances, wherein "related substances" refers to undesired chemical impurities or residual organic solvent.

Advantageously, the novel polymorph of the invention will be free from chemical solvates, for instance  
10 existing as the substantially pure Dihydrate D.

Pharmaceutical formulations containing Dihydrate D should contain less than about 20% Dihydrate B, more preferably less than about 10% Dihydrate B polymorph.

Olanzapine has useful central nervous system  
15 activity. This activity has been demonstrated using well-established procedures, for example, as described in the '382 patent. Dihydrate D provided by the present invention appears to have the same profile of receptor activity and has the same therapeutic uses as olanzapine described in the  
20 '382 patent. Therefore, Dihydrate D is useful for the treatment of schizophrenia, schizophreniform disorders, psychosis, mild anxiety states, and functional bowel disorders.

Dihydrate D is effective over a wide dosage range,  
25 the actual dose administered being dependent on the condition being treated. For example, in the treatment of adult humans, dosages of from about 0.25 to 50 mg, preferably from 1 to 30 mg, and most preferably 1 to 25 mg per day may be used. A once a day dosage is normally  
30 sufficient, although divided doses may be administered. For treatment of central nervous system disorders, a dose range of from 1 to 30 mg, preferably 2.5 to 20 mg per day is suitable.

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A typical example of an x-ray diffraction pattern for Dihydrate D is as follows, wherein d represents the interplanar spacing and  $I/I_1$  represents the typical relative intensities:

d	$I/I_1$
9.4511	100.00
7.7098	14.23
7.4482	22.43
6.9807	5.73
6.5252	5.45
5.7076	4.24
5.5539	1.60
5.223	62.98
4.9803	22.21
4.8908	15.03
4.784	27.81
4.6947	5.15
4.4271	13.00
4.3956	16.63
4.3492	34.43
4.2834	51.38
4.1156	18.32
3.7837	5.30
3.7118	1.56
3.5757	0.71
3.482	9.39
3.3758	24.87
3.3274	13.49
3.2413	5.97
3.1879	1.04
3.135	3.18
3.0979	1.43
3.016	1.95
2.9637	0.48
2.907	2.42
2.8256	7.46
2.7914	3.61
2.7317	1.47
2.6732	5.19
2.5863	10.62

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The x-ray powder diffraction patterns herein were obtained with a copper  $K_\alpha$  of wavelength  $\lambda = 1.541\text{\AA}$ . The interplanar spacings in the column marked "d" are in Angstroms. The typical relative intensities are in the column marked " $I/I_1$ ".

The typical example of an x-ray diffraction pattern for the less stable Dihydrate B polymorph is as follows, wherein d represents the interplanar spacing and  $I/I_1$  represents the typical relative intensities:

10

d	$I/I_1$
9.9045	100.00
6.9985	0.39
6.763	0.17
6.4079	0.13
6.1548	0.85
6.0611	0.99
5.8933	0.35
5.6987	0.12
5.4395	1.30
5.1983	0.67
5.0843	0.24
4.9478	0.34
4.7941	6.53
4.696	1.26
4.5272	2.65
4.4351	2.18
4.3474	1.85
4.2657	0.49
4.1954	0.69
4.0555	0.42
3.9903	0.89
3.9244	1.52
3.8561	0.99
3.8137	1.44
3.7671	0.92
3.6989	1.78

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3.6527	0.60
3.5665	0.34
3.4879	1.41
3.3911	0.27
3.3289	0.20
3.2316	0.31
3.1982	0.19
3.1393	0.35
3.0824	0.18
2.9899	0.26
2.9484	0.38
2.9081	0.29
2.8551	0.37
2.8324	0.49
2.751	0.37
2.7323	0.64
2.6787	0.23
2.6424	0.38
2.5937	0.21

A typical example of an x-ray diffraction pattern for the anhydrous Form II polymorph is as follows, wherein d represents the interplanar spacing and I/I<sub>1</sub> represents the typical relative intensities:

d	I/I <sub>1</sub>
10.2689	100.00
8.577	7.96
7.4721	1.41
7.125	6.50
6.1459	3.12
6.071	5.12
5.4849	0.52
5.2181	6.86
5.1251	2.47
4.9874	7.41
4.7665	4.03
4.7158	6.80
4.4787	14.72

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4.3307	1.48
4.2294	23.19
4.141	11.28
3.9873	9.01
3.7206	14.04
3.5645	2.27
3.5366	4.85
3.3828	3.47
3.2516	1.25
3.134	0.81
3.0848	0.45
3.0638	1.34
3.0111	3.51
2.8739	0.79
2.8102	1.47
2.7217	0.20
2.6432	1.26
2.6007	0.77

As used herein, the term "mammal" shall refer to the Mammalia class of higher vertebrates. The term "mammal" includes, but is not limited to, a human. The term

5 "treating" as used herein includes prophylaxis of the named condition or amelioration or elimination of the condition once it has been established.

The compounds and processes of the present invention are useful for preparing compounds having

10 beneficial central nervous system activity. Certain compounds and conditions within the scope of this invention are preferred. The following conditions, invention embodiments, and compound characteristics listed in tabular form may be independently combined to produce a variety of

15 preferred compounds and process conditions. The following list of embodiments of this invention is not intended to limit the scope of this invention in any way.

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Some preferred characteristics of this invention include the following:

- 5 A) A compound which is the Dihydrate D polymorph of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine (Dihydrate D polymorph);
- B) A compound which is the substantially pure Dihydrate D polymorph;
- 10 C) An aqueous suspension formulation containing Dihydrate D;
- D) A tablet formulation containing substantially pure Dihydrate D which is packaged in a blister packaged under humid conditions;
- 15 E) A consistently stable pharmaceutically elegant aqueous formulation containing substantially pure Dihydrate D;
- F) Substantially pure Dihydrate D is formulated in a unit dosage form;
- 20 G) Substantially pure Dihydrate D is formulated for rapid dissolution;
- H) Substantially pure Dihydrate D is used for treating a condition selected from the group consisting of a psychosis, schizophrenia, a schizophreniform disorder, mild anxiety, and
- 25 acute mania;
- I) An aqueous suspension formulation containing Dihydrate D as an active ingredient wherein such formulation is suitable for injection.
- 30 J) A tablet formulation containing substantially pure Dihydrate D which is package in an air resistant package.

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Depending on the method of administration, the compositions for the treatment of central nervous system conditions may be formulated as tablets, capsules, gel or suspension for transdermal delivery, suspensions or elixirs for oral use or suppositories. If such formulation is a tablet or capsule, then such formulation is most preferably packaged under humid conditions and sealed in an air impermeable sachet or blister pack. Preferably, the compositions are formulated in a unit dosage form, each dosage containing from 0.25 to 100 mg, more usually 1 to 30 mg, of the active ingredient. When a sustained release formulation is desired, the unit dosage form may contain from 0.25 to 200 mg of the active ingredient. A preferred formulation of the invention is an aqueous suspension comprising 0.25 to 75 mg or 1 to 30 mg of active ingredient together with a pharmaceutically acceptable carrier therefor.

The starting materials for the present invention can be prepared by a variety of procedures well known to those of ordinary skill in the art. The material to be employed as starting materials in the process of this invention can be prepared by the general procedure taught by Chakrabarti in U.S. Patent No. 5,229,382 ('382), herein incorporated by reference in its entirety.

The Dihydrate D is prepared by extensive stirring of technical olanzapine, which may be prepared as described by Preparation 1, under aqueous conditions. The term "aqueous conditions" refers to an aqueous solvent which may be either water or a solvent mixture comprising water and an organic solvent which is sufficiently water miscible to allow the required stoichiometric quantity of water to be present in the solvent mixture. If a solvent mixture is utilized, then the organic solvent must be removed, leaving behind the water, and/or replaced with water. The term



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"extensive stirring" shall be from about one (1) hour to about six (6) days; however, the artisan will appreciate that the time will vary with the reaction conditions such as temperature, pressure, and solvent. It maybe preferred to stir for at least about four (4) hours. It is preferred that the aqueous conditions include an aqueous solvent. However, it is to be noted that to form polymorph D, rather than other dihydrate polymorphs, more extensive stirring and/or agitation is required, preferably is excess of 12 hours, more preferably in excess of 24 hours. Further, a wetting agent may be added to the aqueous mixture to speed up the formation of the stable Dihydrate D.

Dihydrate D may be air dried or dried using other standard techniques which are sufficiently mild to avoid desolvation of the Dihydrate D.

The completion of the reaction may be monitored using x-ray powder diffraction and other such methods familiar to the skilled artisan. Several such techniques are described below.

Compound characterization methods include, for example, x-ray powder pattern analysis, thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), titrametric analysis for water, and  $H^1$ -NMR analysis for solvent content.

Accordingly, pharmaceutical compositions comprising Dihydrate D, as active ingredient associated with a pharmaceutically acceptable carrier may be prepared. In making the compositions of the invention conventional techniques for the preparation of pharmaceutical compositions can be used. For example, the active ingredient can usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be solid, semi-

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solid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. The active ingredient can be absorbed in a granular solid container, for example, in a sachet. Some examples of suitable carriers are

5 lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, syrup, methyl cellulose, methyl- and propyl-hydroxy-benzoate, talc, magnesium stearate or mineral oil. The compositions of the invention may, if desired, be

10 formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient. For example, one such quick release formulation is described in US. Patent Nos. 4,305,502 and 4,371,516, hereby incorporated by reference.

15 It is typically preferred that such formulation includes a pharmaceutically acceptable flavoring agent or combinations of such agents, including natural and synthetic flavoring agents such as ASPARTANE® and flavor enhancing agents, such as the commercial product VELTOL® (Pfizer);

20 preservatives such as methyl paraben, propyl paraben and combinations thereof are further preferred.

Another preferred embodiment of this invention is the formulation methods described in U.S. Patent No. 4,758,598, herein incorporated by reference in its entirety.

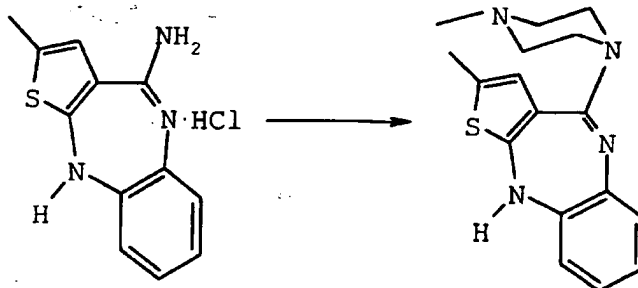
25 A particularly preferred method for treating a subject suffering from or susceptible to a psychotic condition comprises administering an aqueous oral suspension formulation comprising Dihydrate D olanzapine and pharmaceutically acceptable carriers and/or excipients.

30 The following examples are provided for purposes of illustration and are not to be construed as limiting the scope of the claimed invention.

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Preparation 1

## Technical Grade Olanzapine



Intermediate 1

5 In a suitable three neck flask the following was added:

Dimethylsulfoxide (analytical): 6 volumes

Intermediate 1 : 75 g

N-Methylpiperazine (reagent) : 6 equivalents

10 Intermediate 1 can be prepared using methods know to the skilled artisan. For example, the preparation of the Intermediate 1 is taught in the '382 patent.

A sub-surface nitrogen sparge line was added to remove the ammonia formed during the reaction. The reaction was heated to 120°C and maintained at that temperature throughout the duration of the reaction. The reactions were followed by HPLC until  $\leq 5\%$  of the intermediate 1 was left unreacted. After the reaction was complete, the mixture was allowed to cool slowly to 20°C (about 2 hours). The reaction mixture was then transferred to an appropriate three neck round bottom flask and water bath. To this solution with agitation was added 10 volumes reagent grade methanol and the reaction was stirred at 20°C for 30 minutes. Three volumes of water were added slowly over about 30 minutes. The reaction slurry was cooled to zero to 5°C and stirred

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for 30 minutes. The product was filtered and the wet cake was washed with chilled methanol. The wet cake was dried in vacuo at 45°C overnight. The product was identified as technical olanzapine.

5

Yield: 76.7%; Potency: 98.1%

#### Example 1

##### Dihydrate D

10

A 100 g sample of technical grade olanzapine (see Preparation 1) was suspended in water (500 mL). The mixture was stirred at about 25°C for about 5 days. The product was isolated using vacuum filtration. The product was identified as Dihydrate D olanzapine using x-ray powder analysis. Yield: 100 g. TGA mass loss was 10.2%.

#### Example 2

20

A sample of gelatin powder (1 g) is admixed with maltodextran (2 g), gelatin A (0.5 g); sucrose (2 g) and ASPARTANE® (1 g). Distilled water is added to the mixture to about 100 mL total volume. The mixture is stirred and heated to about 60°C. The mixture should be heated until it appears to be a clear solution. The mixture is cooled to about 37°C. Blister molds are prepared by rinsing with a solution of lecithin (about 10%) in about 190 proof grain alcohol. The molds so prepared are dried at room temperature. An aliquot of the cooled mixture is added to each compartment of the mold. The mold containing the mixture is cooled to a temperature of about -10°C or lower for about 40 minutes. The mold containing the mixture is removed from the < -10°C environment and about 20 mg of

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anhydrous olanzapine is added to the surface of each tablet within the mold. The mold should remain protected from thawing. The mold containing the mixture and olanzapine is again cooled to about -10°C for about 40 minutes.

5           The mold is removed from the cooled about -10°C environment and an additional aliquot of the gelatin based mixture (to which no olanzapine has been added) is added to the surface of each compartment of the mold prepared as described *supra*. The mold is again cooled to about -10°C  
10   for about 40 minutes.

          The tablets are removed from the mold to a mesh plastic bag. The bag and its contents are hermetically sealed in a container of anhydrous ethyl alcohol and maintained at a temperature of -20°C. The tablets are  
15   maintained in the hermetically sealed bag until the tablets are completely dehydrated. The dehydration continues until no odor or other evidence of alcohol can be detected on the tablets. The formulation is studied using x-ray powder diffraction techniques to assure that substantially pure  
20   Dihydrate D is present.

### Example 3

Suspensions each containing 5 mg of medicament per 5 ml dose are as follows:

25

	Per 5 ml of <u>suspension</u>
Dihydrate D	5 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 ml
Benzoic acid solution	0.10 ml
Flavor	q.v.
Color	q.v.
Water	q.s. to 5 ml

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The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethylcellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color is diluted with some of the water and added to the past with stirring. Sufficient water is then added to produce the required volume.

Example 4

10                    Suspensions each containing 20 mg of medicament per 5 ml dose are as follows:

	Per 5 ml of <u>suspension</u>
Dihydrate D	20 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 ml
Benzoic acid solution	0.10 ml
Flavor	q.v.
Color	q.v.
Water	q.s. to 5 ml

15                    The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethylcellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color is diluted with some of the water and added to the paste with stirring. Sufficient water is then added to produce the required volume.

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Claims

1. Dihydrate D olanzapine polymorph having a typical x-ray powder diffraction pattern as represented by:  
5 the following interplanar spacings (d) as set forth in Table 1:

Table 1

d
9.4511
7.7098
7.4482
6.9807
6.5252
5.7076
5.5539
5.223
4.9803
4.8908
4.784
4.6947
4.4271
4.3956
4.3492
4.2834
4.1156
3.7837
3.7118
3.5757
3.482
3.3758
3.3274
3.2413
3.1879
3.135
3.0979
3.016
2.9637
2.907
2.8256
2.7914
2.7317
2.6732
2.5863

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2. A Dihydrate D polymorph as claimed in Claim 1 further characterized by substantially the following x-ray powder diffraction pattern wherein d represents the interplanar spacing and I/I<sub>1</sub> represents the typical relative intensities:

d	I/I <sub>1</sub>
9.4511	100.00
7.7098	14.23
7.4482	22.43
6.9807	5.73
6.5252	5.45
5.7076	4.24
5.5539	1.60
5.223	62.98
4.9803	22.21
4.8908	15.03
4.784	27.81
4.6947	5.15
4.4271	13.00
4.3956	16.63
4.3492	34.43
4.2834	51.38
4.1156	18.32
3.7837	5.30
3.7118	1.56
3.5757	0.71
3.482	9.39
3.3758	24.87
3.3274	13.49
3.2413	5.97
3.1879	1.04
3.135	3.18
3.0979	1.43
3.016	1.95
2.9637	0.48
2.907	2.42
2.8256	7.46
2.7914	3.61



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2.7317	1.47
2.6732	5.19
2.5863	10.62

3. Dihydrate D of Claim 1 wherein the Dihydrate D is substantially pure.

5 4. Dihydrate D of Claim 2 wherein the Dihydrate D is substantially pure.

10 5. Dihydrate D of Claim 2 wherein "substantially pure" refers to less than 2% Dihydrate B wherein Dihydrate B has a typical x-ray powder diffraction pattern as represented by the following interplanar spacings (d) as set forth in Table 2:

Table 2

d	I/I <sub>1</sub>
9.9045	100.00
6.9985	0.39
6.763	0.17
6.4079	0.13
6.1548	0.85
6.0611	0.99
5.8933	0.35
5.6987	0.12
5.4395	1.30
5.1983	0.67
5.0843	0.24
4.9478	0.34
4.7941	6.53
4.696	1.26
4.5272	2.65
4.4351	2.18
4.3474	1.85
4.2657	0.49
4.1954	0.69
4.0555	0.42

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3.9903	0.89
3.9244	1.52
3.8561	0.99
3.8137	1.44
3.7671	0.92
3.6989	1.78
3.6527	0.60
3.5665	0.34
3.4879	1.41
3.3911	0.27
3.3289	0.20
3.2316	0.31
3.1982	0.19
3.1393	0.35
3.0824	0.18
2.9899	0.26
2.9484	0.38
2.9081	0.29
2.8551	0.37
2.8324	0.49
2.751	0.37
2.7323	0.64
2.6787	0.23
2.6424	0.38
2.5937	0.21

6. Dihydrate D of **Claim 1** wherein Dihydrate D is a stable crystalline pharmaceutically elegant polymorph.

5           7. Dihydrate D of **Claim 2** wherein dihydrate D is a stable crystalline pharmaceutically elegant polymorph.

8. A pharmaceutical formulation comprising as an active ingredient a compound of **Claim 1** associated with one or more pharmaceutically acceptable carriers, diluents, or excipients therefor.

10

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9. A pharmaceutical formulation comprising as an active ingredient a compound of **Claim 2** associated with one or more pharmaceutically acceptable carriers, diluents, or excipients therefor.

5

10. A formulation of **Claim 8** wherein the formulation is an aqueous suspension.

11. A formulation of **Claim 8** wherein the  
10 formulation is a tablet.

12. A pharmaceutical formulation comprising as an active ingredient a compound of **Claim 3** associated with one or more pharmaceutically acceptable carriers, diluents, or  
15 excipients therefor.

13. A formulation of **Claim 12** wherein the formulation is an aqueous suspension.

20 14. A method for treating a psychotic condition in a mammal comprising administering an effective amount of a compound of **Claim 1**.

25 15. A method for treating a condition selected from the group consisting of anxiety, schizophrenia, schizophreniform disorder, a functional bowel disorder, and psychosis in a mammal comprising administering an effective amount of a compound of **Claim 1**.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US97/16586

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC(6) :A61K 31/395; C07D 243/10, 243/38 US CL :514/220; 540/557 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) U.S. : 514/220; 540/557  Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched None  Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CAS ONLINE		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y, P	US 5,631,250 A (BUNNELL et al.) 20 May 1997, col. 2, lines 1-63.	1-15
Y	US 5,229,382 A (CHAKRABARTI et al.) 20 July 1993, col. 2, lines 20-38.	1-15
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* "A"	Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"B"	earlier document published on or after the international filing date	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	
"P"	document published prior to the international filing date but later than the priority date claimed	*A* document member of the same patent family
Date of the actual completion of the international search 07 NOVEMBER 1997		Date of mailing of the international search report 30 JAN 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230		Authorized officer MATTHEW V. GRUMLING Telephone No. (703) 308-1235